Toward More Aggressive Management of Neuroendocrine Tumors: Current and Future Perspectives

Moderator:
Ashley Grossman, MD, FRCP
Professor of Neuroendocrinology
William Harvey Research Institute
Barts and the London School of Medicine and Dentistry
St. Bartholomew's Hospital
London, United Kingdom

Panel (cont):
Prof. Massimo Falconi, MD
Department of Surgery
University of Verona
Verona, Italy

Bertram Wiedenmann, MD, PhD
Professor of Internal Medicine and Gastroenterology
Chairman, Department of Hepatology, Gastroenterology, and Metabolic Diseases
Charité Medical School, Campus Virchow-Klinikum
Humboldt-University
Berlin, Germany
Incidence of NETs Increasing

NETs — Second Most Prevalent Gastrointestinal Tumor

NET Prevalence in the United States, 2004

29-year limited duration prevalence analysis based on SEER [Surveillance, Epidemiology, and End Results].

Many NETs Are Diagnosed When Metastatic

- Localized: 50%
- Regional: 24%
- Distant: 27%

Diagnostic Challenges in NET

- Heterogeneous group of tumors
- Wide variety of clinical presentations
- Late presentation
- Different terminology and classifications
- Histologic diagnosis may be difficult
- Variety of therapeutic options/approaches
Classification of NET

Classification as functional vs nonfunctional

Classification by site of origin
- Nearly identical characteristics on routine histologic evaluation, but different responses to therapeutic agents

Classification by tumor stage
- TNM
- AJCC
- ENETS

TNM: tumor, lymph nodes, metastasis; AJCC: American Joint Committee on Cancer; ENETS: European Neuroendocrine Tumor Society
Classification of NET (cont)

Histologic classification

- Well-differentiated malignancies
- Highly aggressive malignancies:
  - Poorly differentiated tumors with a high grade (grade 3) or
  - Mitotic count > 20 per 10 HPFs, or
  - Ki-67 proliferation index > 20%

Molecular classification

- MEN 1 & 2, tuberous sclerosis, VHL

HPF: high-power fields; MEN: multiple endocrine neoplasia; VHL: Von Hippel-Lindau disease
## Grading Proposal for NETs of Ileum, Appendix, Colon, and Rectum

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic count (10 HPF)*</th>
<th>Ki-67 index (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

*10 HPF: 2 mm², at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.

†Ki-67, MIB1 antibody; % of 2000 tumor cells in areas of highest nuclear labeling.

NET Survival by Histology

**Carcinoid / Islet cell**
- Well differentiated: 124 months, 95% CI 101 to 147
- Unspecified grade: 129 months, 95% CI 124 to 134
- Moderately differentiated: 64 months, 95% CI 56 to 72

**Neuroendocrine**
- Poorly differentiated: 10 months, 95% CI 9 to 11
- Anaplastic: 10 months, 95% CI 9 to 11
- Unspecified grade: 10 months, 95% CI 9 to 11

Assessment of NET: Factors to Consider

Clinical picture

Hormonal peptides

Imaging
- Anatomical imaging
- Molecular imaging
  - SSR scanning
  - Octreotide SPECT/CT
  - New tracers (e.g., 68Ga-DOTA-octreotide PET)

Histology

CT: computed tomography; PET: positive electron tomography; SPECT: single-photon emission computed tomography; SSR: somatostatin receptor
Treatment Goals in NET

- Total eradication by surgery
- Control of tumor growth
- Alleviation of clinical symptoms
- Improving and preserving quality of life
Factors in Treatment Decisions in NETs

- Treatment decisions require discussion by a multidisciplinary team
- Options may depend on:
  - Type of NET
  - TNM stage
  - Tumor grade
  - Extent of disease, including liver disease
  - Functional status of tumor
  - Patient: organ function, ECOG PS, comorbidity
  - Access to various options

ECOG: Eastern Cooperative Oncology Group; PS: performance status
Treatment Options in NET

Surgery

Embolization (± chemotherapy)

Medical treatment
- Somatostatin analogues
- Alpha interferon therapy
- Chemotherapy
- PRRT
- Biological targeted agents

PRRT: peptide receptor radionuclide therapy
Surgical Options in NET

Radical surgery
- Complete resection of entire tumor even in presence of liver metastases

Debulking surgery
- Always employed in functional carcinomas, when medical therapies do not control symptoms
- Resection of at least the primary tumor and liver metastases (suitable procedure when at least 90% of the tumor is resectable)

Palliative surgery
- No resection
- Biliary, gastric, or digestive bypasses in case of obstruction when tumor is unresectable
# Radical Surgery in NET: Consider Likelihood of Malignancy

<table>
<thead>
<tr>
<th>Site</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midgut</td>
<td>Same as in carcinoma; always considered to be malignant</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Atypical resection:</td>
<td>Typical resection, same as in carcinoma:</td>
</tr>
<tr>
<td></td>
<td>✔️ Enucleation</td>
<td>✔️ Pancreatic duodenectomy</td>
</tr>
<tr>
<td></td>
<td>✔️ Middle pancreatectomy</td>
<td>✔️ Left pancreatectomy</td>
</tr>
</tbody>
</table>

In absence of liver metastases or nearby structure invasion.
Debulking Procedures in NET

Aims

• Reduce mechanical symptoms
• Preserve one target organ (the liver) for further therapies
• Improve survival

“Weapons”

• Surgery
• TACE
• RFTA
• Combination of these procedures

RFTA: radiofrequency thermal ablation; TACE: transarterial (chemo) embolization
Prognosis and Clinical Course of Patients With Liver Metastatic Midgut NETs: A Retrospective European Study

Survival of patients with bowel bypass vs failed resection, no resection, or resection

Log rank (Mantel-Cox) $P < .000$

Primary removed
- Bowel bypass ($n = 12$)
- Failed resection ($n = 17$)
- No resection ($n = 80$)
- Resected ($n = 210$)

Challenges in Treatment of Metastatic NETs

- Over half of NET patients are diagnosed at metastatic stage\(^{[a]}\)
- Metastatic NETs are incurable and most patients will succumb to the disease
- No new antitumor agents approved in the last 30 years
- Lack of level 1 evidence from controlled randomized trials to guide treatment of patients with NETs

Symptomatic Treatment of NETs

• Symptoms of patients with metastatic NETs include:[a]
  – Diarrhea, flushing, bronchoconstriction, cardiac disease, hypoglycemia, gastric ulcer, skin rash

• 80% to 90% of patients with NETs express somatostatin receptors, which can be targeted[b]

• Somatostatin analogues effective in reducing hormonal secretion and controlling symptoms of NETs[a]
  – Most common adverse events: diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis

Complete or Partial Symptom Control With Octreotide LAR in NET

- **Flushing**: n = 53
  - > 50% improvement: 89%
  - Complete improvement: 57%

- **Diarrhea**: n = 49
  - > 50% improvement: 74%
  - Complete improvement: 25%

- **Urinary 5-HIAA**: n = 57
  - > 50% improvement: 68%
  - Complete improvement: 5%

5-HIAA: 5-hydroxyindoleacetic acid; LAR: long-acting release

PROMID: Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Midgut NETs

Primary endpoint: TTP
Secondary endpoints: Objective response rate, OS, quality of life, safety

CT: computed tomography; IM: intramuscular; MRI: magnetic resonance imaging; OS: overall survival; PROMID: Placebo-controlled prospective Randomized study on the antiproliferative efficacy of Octreotide LAR in patients with metastatic neuroendocrine MIDgut tumors; TTP: time to progression

PROMID: Octreotide LAR Slows Disease Progression in Midgut NETs

TTP in Midgut NET

Octreotide LAR vs placebo $P < .001$
HR: 0.34 (95% CI: 0.20–0.59)

Octreotide LAR (n = 42)
Median 14.3 months

Placebo (n = 43)
Median 6.0 months

Based on conservative ITT analysis

HR: hazard ratio; ITT: intent-to-treat

Systemic radiotherapy targeting somatostatin receptors

Compounds vary by isotope and carrier molecule
- Most common isotopes used are $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE

Positive somatostatin receptor scan required prior to treatment

Promising results with Yttrium-90 edotreotide[1] and $^{177}$Lu DOTATATE[2] in single-arm phase 2 trials

No randomized controlled trials to date

Systemic Chemotherapy in Pancreatic NET: Streptozocin and Temozolomide

- Have shown ability to control symptoms and proliferation in G1/2 pancreatic NETs
- Considered second-line agents because of more side effects than first-line SSAs
- Combinations studied to date include:
  - Streptozocin + 5-FU and/or doxorubicin
  - Temzolomide + thalidomide, bevacizumab, or capecitabine
- Some combinations show promising RRs, but quality of existing data do not allow registration

FU: fluorouracil; G1/2: grade 1/2; RR: response rate; SSA: somatostatin analogue
Poorly Differentiated Neuroendocrine Carcinoma (NEC): Cisplatin + Etoposide

- Tumors mainly in upper GI and colon
  - Must be considered separately from other tumors
  - Treated similarly to SCLC

- Small studies (N = 18 to 41) with cisplatin + etoposide:\(^1,2\)
  - Objective response similar to that in SCLC (42% to 54%)
  - Median survival also low (15 to 19 mo)

---


SCLC: small-cell lung cancer
Rationale for the Use of Angiogenesis Inhibitors in NETs

Dense vascularization is a key feature of NETs

VEGF and VEGF-R are overexpressed in NETs

Elevated circulating VEGF correlates with tumor progression

VEGF: vascular endothelial growth factor

# Efficacy and Tolerability of Angiogenesis Inhibition in NETs

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Study Phase</th>
<th>Target</th>
<th>N</th>
<th>PD entry criteria?</th>
<th>RR</th>
<th>PFS (months)</th>
<th>AEs</th>
<th>Drop-out rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vatalanib&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1/2</td>
<td>VEGFR-1,2,3 (PDGFR, c-kit)</td>
<td>23</td>
<td>Yes</td>
<td>9% PR/MR</td>
<td>7.5</td>
<td>35%: G3-4</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
<td></td>
<td>16</td>
<td>No</td>
<td>Ø PR</td>
<td>ND</td>
<td>61%: G3</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endostatin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2</td>
<td>endogenous inhibitor</td>
<td>42</td>
<td>No</td>
<td>Ø PR</td>
<td>5.8*</td>
<td>52%: G3-4</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib&lt;sup&gt;4&lt;/sup&gt;</td>
<td>2</td>
<td>C-RAF, B-RAF VEGFR-2, -3, PDGFR-β, KIT</td>
<td>82</td>
<td>No</td>
<td>9% PR</td>
<td>7.8&lt;sup&gt;†&lt;/sup&gt;</td>
<td>43%: G3-4</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10% MR</td>
<td>11.9*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SD not rep.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3</td>
<td>VEGFR, PDGFR, c-kit</td>
<td>86</td>
<td>Yes</td>
<td>2.3% CR</td>
<td>11.4</td>
<td>26.5%: G3-4</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7% PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.8% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab + octreotide</td>
<td>2</td>
<td>VEGF + SSTR</td>
<td>22</td>
<td>No</td>
<td>18% PR</td>
<td></td>
<td>5%: G3-4</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77% SD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PNET; †GI NETs

HTN: hypertension; MR: minor response; ND: not determined; PDGFR: platelet-derived growth factor receptor; PR: partial response; SD: stable disease; SSTR: somatostatin receptor; VEGFR: vascular endothelial growth factor receptor

Everolimus (RAD001): An Oral mTOR Pathway Inhibitor

- Oral mTOR inhibitor with broad antitumor activity and antiangiogenic activity\[a-d]\n- Daily dosing with everolimus 5-10 mg resulted in continuous inhibition of mTOR activity\[d,e]\n
mTOR: mammalian target of rapamycin

RADIANT-1: RAD001 +/- Octreotide LAR in Pancreatic NET: Open-Label Phase 2 Study

**PFS by Central Review**

**Everolimus**
37.2% grade 3-4 AEs

- Median PFS: 9.7 mo
- Patients at risk: 115

**Everolimus + octreotide LAR**
33.0% grade 3-4 AEs

- Median PFS: 16.7 mo
- Patients at risk: 45

RADIANT 3: BSC + Everolimus or Placebo in Progressive Advanced pNET

Primary endpoint: PFS

Kaplan-Meier median PFS
Everolimus: 11.04 mo
Placebo: 4.60 mo
HR: 0.35 (95% CI 0.27 to 0.45)
P < .0001

Number of patients “at risk”
<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>207</td>
<td>203</td>
</tr>
<tr>
<td>2</td>
<td>189</td>
<td>177</td>
</tr>
<tr>
<td>4</td>
<td>153</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>114</td>
<td>52</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- *P* value obtained from stratified one-sided log-rank test
- HR obtained from stratified unadjusted Cox model

Phase 3 Trial: Sunitinib vs Placebo in Advanced pNET

Study halted prior to complete accrual due to treatment benefit
Unplanned Kaplan-Meier PFS analysis

\[ P < .001; \text{HR: 0.397} \]
\[ (95\% \text{ CI: 0.243 to 0.649}) \]

Sunitinib: PFS 11.1 mo
Placebo: PFS 5.5 mo

Medical Therapy in NETs: Summary

- Numerous agents now available
- Streptozocin and temozolomide have shown response in NETs
  - Lack strong evidence base
- Good data with everolimus, octreotide LAR, and sunitinib
- Options for poorly differentiated tumors:
  - Oxaliplatin
  - Cisplatin + etoposide
Future Directions

- Biomarkers and molecular imaging for evaluation of therapeutic response
- Personalized treatment based on molecular genetics and tumor biology
  - WHO and TNM classification
- Molecularly targeted treatment will be the future:
  - Targeted agents
  - PRRT
  - Combinations of traditional cytotoxics with targeted agents
  - Combinations of targeted agents
Take-Home Messages

Role of Pathology in NET Management
- Critical to appropriate management decisions in NETs
- Includes staging, grading, differentiation, site of origin, Ki-67 status, histologic characteristics
- Drives therapeutic strategy

When to Consider Surgery
- Radical surgery should take priority when feasible
- Surgeon must coordinate with oncologist in advanced disease
Take-Home Messages (cont)

When and How to Initiate Treatment in NETs

• Multidisciplinary decision-making process including pathologist
• Factors to consider include:
  – Where is primary site?
  – Progressive or stable disease?
  – Stage of disease?
Conclusions

- Precise pathology is crucial in management of NETs
- Surgical intervention is a key step in NET management, even when not curative
- Multidisciplinary team approach
  - Introduce treatment at appropriate time
  - Customize treatment based on patient and disease factors